REMARKS

Claims 99-107, 110-125 and 178-199 are pending. Claims 99-107, 110-113, 118-123 and 178-199 are under examination. Claim 102 has been amended to correct antecedent basis. Accordingly, this amendment does not raise an issue of new matter and entry thereof is respectfully requested.

Applicants appreciate the time and helpful discussion between Examiner Yao and Applicants' representative in the telephonic interview on June 26, 2007. It is believed that the response addresses the issues discussed in the interview.

Regarding the Sequence Requirements

In the Office Action, it is indicated that the application fails to comply with the requirements of 37 C.F.R. § 1.821(a)(1) and (a)(2). In particular, the Office Action indicates that sequences on page 23, lines 25 and 27, and page 57, line 22, require SEQ ID NOS. Applicants respectfully disagree. In particular, Applicants respectfully point out that those sequences referred to in the Office Action contain D amino acids, and amino acid sequences that include D amino acids are excluded from the requirements of being identified with a SEQ ID NO.

37 C.F.R. 1.821(a)(2) states as follows:

> (2) Amino acids: Amino acids are those L-amino acids commonly found in naturally occurring proteins and are listed in WIPO Standard ST.25 (1998), Appendix 2, Table 3. Those amino acid sequences containing D-amino acids are not intended to be embraced by this definition. [emphasis added]

Applicants respectfully submit that the sequences on page 23, lines 25 and 27, and page 57, line 22, which contain D amino acids, do not require a SEQ ID NO and, therefore, the specification and Sequence Listing previously submitted August 25, 2003, satisfy the requirements of 37 C.F.R. § 1.821(a)(1) and (a)(2). Accordingly, Applicants respectfully request that the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures be withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 102-113, 118-123 and 188-199 under 35 U.S.C. § 112, second, paragraph, as allegedly indefinite is respectfully traversed. The Office Action indicates that claim 102 is unclear for the phrase "said peptide" in that it lacks antecedent basis. Claim 102 has been amended to correct antecedent basis as requested by the Examiner. Accordingly, Applicants respectfully submit that claim 102 and its dependent claims are clear and definite and request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 99-107, 110-113, 118-123, 178-186 and 188-198 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description is respectfully traversed. Applicants respectfully maintain, for the reasons of record, that the specification provides sufficient description and guidance for the claimed peptides and conjugates.

As discussed in the previous response filed September 18, 2006, Applicants respectfully maintain that the specification teaches a peptide "comprising" CREKA (SEQ ID NO:1). In particular, the CREKA (SEQ ID NO:1) peptide was identified using a phage display library that was injected into mice and recovered from breast tumor tissue (Example 1, pages 67-70). A peptide library was used, with the peptide expressed on the surface of the phage as a fusion with a phage protein, in particular the product of gene III. Such a peptide-gene III fusion protein is exemplary of a peptide "comprising" CREKA (SEQ ID NO:1).

Moreover, Applicants respectfully submit that the comments in the paragraph bridging pages 5-6 of the Office Action regarding potential size limitations of inserts in phage display mischaracterize the cited reference by Smith et al., Chem. Rev. 97:391-410 (1997). The Office Action states:

> In addition, Smith et al. (Chem Rev, vol 97, page 391-410) teach phage display system for screening a peptide comprising homing molecule and indicate when the gene display a relative large foreign peptide (more than eight amino acids), it will not support phage production and produce mosaic particles (page 393, col 2). Thus, one skilled in the art has recognized that the peptides comprising homing peptide in phase [sic] display is limited to the certain size and/or the certain sequence in order to perform the certain function. Instant specification does not

> provide any other peptides having 6-100 amino acids comprising CREKA (SEQ ID NO:1) could be fused to Gene III and home to tumor vasculature and bind to collagen. [emphasis in original]

Turning to page 393, column 2 of Smith et al., the reference states in the first complete paragraph:

> Figure 1 diagrams the ways that foreign peptides have been fused to these proteins. Until recently, foreign peptides have been fused to regions of pVIII and pIII that were known to be exposed to the exterior: the N-terminus of pVIII[23] and the N-terminus and middle of pIII.[24,25] In some pIII vectors, the foreign peptide replaces the N-terminal domain of pIII (the third diagram in Figure 1), yielding a hybrid protein that can be incorporated into the virion but must be supplemented by complete pIII molecules if the virion is to be infective (see type 3+3 systems in the next subsection); infective virions in this case are thus mosaics with two types of pIII molecule. Similarly, when pVIII displays a relatively large foreign peptide (more than about eight amino acids), it will not support phage production unless it is supplemented by wild-type pVIII molecules, again yielding mosaic particles.[26-29] [emphasis added]

Clearly the statement in the Office Action that "when the gene display a relative large foreign peptide (more than eight amino acids), it will not support phage production and produce mosaic particles" is a mischaracterization of the passage from Smith et al. First, Smith et al. does not teach that a foreign peptide of "more than eight amino acids" will not support phage production. To the contrary, Smith et al. describes that for gene VIII (not gene III), displaying a peptide of more than about eight amino acids will not support phage production unless it is supplemented by wild type pVIII molecules. The supplementation with wild type pVIII results in mosaics displaying both wild type pVIII and pVIII fusions with displayed peptides. Similarly, certain forms of gene III fusions, in which the foreign peptide replaces the N-terminal domain of pIII, also requires coexpression with complete pIII molecules, resulting in mosaic virions. In both cases, the mosaics support phage production, contrary to the erroneous assertion in the Office Action. Thus, Smith et al. provides no teaching that, in phage display, peptide fusions larger than 8 amino acids will not support phage production, as asserted in the Office Action. To the contrary, Smith et al. teaches a range of peptide sizes displayed as pIII and pVIII fusions, including up to 40-mer sequences (see Table 1, page 395). Therefore, Applicants respectfully submit that the comments in the Office Action regarding Smith et al. are not relevant to the claimed CREKA polypeptides that home to tumor vasculature and selectively bind collagen and

further maintain that the gene III fusion peptides disclosed in the specification are exemplary of peptides "comprising" the recited amino acid sequence.

Regarding the recited size limitations and functional activity, Applicants respectfully maintain that the claims do not include non-functional variants but only those peptides or conjugates comprising CREKA (SEQ ID NO:1), having a length of less than 100 residues, and that selectively home to tumor vasculature and selectively bind collagen. Thus, the claims are directed to peptides and conjugates and specifically recite size limitations, having a length of less than 100 residues or shorter recited sizes, and functional activity, selectively homing to tumor vasculature and selectively binding collagen, of the peptides comprising CREKA (SEQ ID NO:1). As discussed in the telephonic interview, Applicants respectfully submit that it is well known to the skilled artisan how to add amino acids to the amino or carboxyl terminus of a CREKA peptide and test the ability of the peptide to selectively home to tumor vasculature and selectively bind collagen using, for example, the methods taught in the specification (see Examples 1-3, pages 67-78). Furthermore, as discussed above and in the previous response filed September 18, 2006, the specification teaches that the peptides were identified as tumor homing molecules using phage display, in which a peptide library was expressed as a fusion protein on the surface of a phage (see Examples 1 and 2, pages 67-72). Thus, the peptides were identified as tumor homing peptides comprising the phage coat protein to which the peptides were fused and therefore exemplify peptides "comprising" the recited peptide sequences that home to tumor vasculature, as recited in the claims.

Applicants respectfully submit that the specification provides sufficient description and guidance for the claimed peptides and conjugates. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The rejection of claims 99-107, 110-113, 118-123, 178-186 and 188-198 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed. Applicants respectfully submit that the specification provides sufficient description and guidance to enable the claimed peptides and conjugates.

Regarding the recited size limitations and functional activity, as discussed above, Applicants maintain that the claims do not include non-functional variants but only those

peptides or conjugates comprising CREKA (SEQ ID NO:1), having a length of less than 100 residues, and that selectively home to tumor vasculature and selectively bind collagen. In the Office Action on page 8, Burgess et al., J. Cell Biol. 111:2129-2138 (1990), and Lazar et al., Mol. Cell. Biol. 8:1247-1252 (1988), are asserted to describe amino acid substitutions, including single amino acid substitutions, that affect biological activity of a protein. However, Applicants respectfully submit that Burgess et al. and Lazar et al., at best, appear to describe amino acid substitutions of the binding site of acidic fibroblast growth factor (FGF) or transforming growth factor α (TGFα), respectively (see abstract of both references). In contrast, the claimed peptides and conjugates recite the CREKA sequence and require the functional activity of the CREKA peptide of selective homing to tumor vasculature and selective binding to collagen. Accordingly, Applicants respectfully submit that the description in Burgess et al. and Lazar et al. of amino acid substitutions in the binding site of acidic FGF and TGFα that alter activity are not relevant to the claimed peptides and conjugates, which recite the CREKA peptide that has the functional activity of selectively homing to tumor vasculature and selectively binding collagen.

Regarding the Shimkets et al. reference, WO 2001/192523, the Office Action asserts that this reference describes a peptide comprising CREKA but does not record the peptide as having the function of homing to tumor vasculature and binding to collagen. Applicants respectfully submit that the assertion in Shimkets et al. that the 11,491 open reading frames identified can be used in the treatment of a laundry list of diseases and conditions is not relevant to the claimed peptides, which recite the specific structure of the CREKA peptide and the functional activity of selectively homing to tumor vasculature and selectively binding collagen.

As discussed above and in the telephonic interview, Applicants respectfully maintain that it is well known to the skilled artisan how to add amino acids to the amino or carboxyl terminus of a CREKA peptide and test the ability of the peptide to selectively home to tumor vasculature and selectively bind collagen using, for example, the methods taught in the specification (see Examples 1-3, pages 67-78). Furthermore, as discussed in the previous response filed September 18, 2006, the specification teaches that the peptides were identified as tumor homing molecules using phage display, in which a peptide library was expressed as a fusion protein on the surface of a phage (see Examples 1 and 2, pages 67-72). Thus, the peptides were identified as tumor homing peptides comprising the phage coat protein to which the peptides were fused and

therefore exemplify peptides "comprising" the recited peptide sequences that home to tumor vasculature, as recited in the claims. Accordingly, Applicants respectfully maintain that one skilled in the art would readily understand how to make and use the claimed peptides "comprising" CREKA (SEQ ID NO:1) because it would be routine to make peptides comprising CREKA and having a length of less than 100 amino acids and test for the recited activities of selectively homing to tumor vasculature and selectively binding collagen, as recited in the claims.

In the paragraph bridging pages 7-8, the Office Action refers to Mathews and Van Holde, Biochemistry pp. 165-171 (1996), as describing that proteins are folded 3-dimensional structures and that the function and stability of a protein relates to a specific conformation. Applicants respectfully maintain, as discussed in the previous response filed September 18, 2006, that any concerns regarding the possibility that very large peptides "comprising" CREKA (SEQ ID NO:1) may have secondary structure and assume conformations that mask the binding activity of the CREKA (SEQ ID NO:1) sequence are not relevant to the claims, which recite that the largest peptide "comprising" CREKA (SEQ ID NO:1) has a length of less than 100 residues and selectively homes to tumor vasculature and selectively bind collagen. Furthermore, as discussed above, one skilled in the art would readily know how to add amino acids to the amino or carboxyl terminus of a CREKA peptide and test the ability of the peptide to selectively home to tumor vasculature and selectively bind collagen using, for example, the methods taught in the specification (see Examples 1-3, pages 67-78). The claims are thus directed to peptides and conjugates and specifically recite size limitations, having a length of less than 100 residues or shorter recited sizes, and functional activity, selectively homing to tumor vasculature and selectively binding collagen, of the peptides comprising CREKA (SEQ ID NO:1), and Applicants respectfully submit that one skilled in the art would readily understand how to make and use the peptides and conjugates, as claimed.

Applicants respectfully submit that the specification provides sufficient description and guidance to enable the claimed peptides and conjugates. Accordingly, Applicants respectfully request that this rejection be withdrawn.

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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